Cancer's SOS

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RAS proteins regulate growth, survival and proliferation of cells in their active state. However, the uncontrolled activation of RAS causes approximately a third of all tumors and helps cancerous cells evade anti-cancer drugs. Thus RAS is an important target for effective anti-cancer treatments.

RAS proteins become "active" through the exchange of guanine nucleotides (GTP for GDP), which is catalyzed by guanine nucleotide exchange factor proteins such as Son of Sevenless homologue 1 (SOS1).

Stephen Fesik, Ph.D., and colleagues previously discovered small molecules that bind to SOS1 and activate nucleotide exchange on RAS.

Now, in the journal *ACS Chemical Biology*, they report that these compounds modulate two downstream signaling pathways via independent cellular responses. They also identify a potent SOS1 agonist that rapidly elicits on-target molecular effects at substantially lower concentrations than those causing off-target effects.

The discovery, they concluded, will allow them to further define the on-target utility of SOS1 agonists and to advance their drug-discovery efforts.

More information: Denis T. Akan et al. Small Molecule SOS1 Agonists Modulate MAPK and PI3K Signaling via Independent Cellular Responses, *ACS Chemical Biology* (2019). DOI: 10.1021/acschembio.8b00869

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